REMARKS

Claims 1 – 19 are under examination and all have been rejected.

Priority Claim

Applicant has amended the priority claim on page 1 of the application to reflect that the parent application has now issued as a U.S. Patent.

Rejection Based on Obviousness-type Double Patenting

Claims 11-16 were rejected on grounds of obviousness-type double patenting over claims 1-12 of U.S. Patent No. 6,355,239.

In response, Applicants enclose herewith a Terminal Disclaimer and accompanying fee for a small entity.

Rejection Under 35 U.S.C. 112, ¶1

Claims 1-19 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enabling requirement. The Examiner contends, *inter alia*, that the application fails to disclose any working examples dealing with muscle.

Claims 1-10 were rejected as encompassing a method for promoting hematopoietic or progenitor cell engraftment in an animal by administering non-autologous mesenchymal stem cells.

In response, Applicants note that a working example of all embodiments is not required for patentability.

Further, much of the Examiner's arguments are directed against xenotransplantation, in that claim 1 is drawn to use of non-autologous MSCs. Applicants have amended claim 1 to recite that the MSCs are allogeneic (which means between animals of the same species) and that the recipient is a mammal (since the working examples utilize mammals). Thus, problems of xenotransplantation of MSCs are not relevant.

In addition, Applicants have further amended claim 1 to recite that the method is useful for bone marrow tissue transplantation. This amendment is supported in the specification at page 10, lines 26-27, at page 14, line 27, at page 20, lines 7-9, at page 26, line 9 and line 21, at page 34, line 15 and at page 39, line 14.

In addition, the Examiner argues that Applicants provide no working examples where hematopoietic or progenitor cell engraftment is enhanced by MSC transplantation. In response, Applicants have amended claim 1 to recite that the method is conducted in a mammal and further direct the Examiner's attention to the application at page 12, lines 12-24 (see parent patent 6,355,239 at column 6, line 58, over to column 7, line 7), and at page 26, lines 20-22, and page 27, lines 7-9 (the '239 patent at column 14, lines 42-44 and 63-67) and at page 39, lines 13-19 (the '239 patent at column 21, line 48, over to column 22, line 6).

As stated in the parent '239 patent, at column 21, lines 48-50, "These results (of Example 4) demonstrate that allogeneic MSCs can support the rapid engraftment of bone marrow hematopoietic cells." Thus, Applicants have well described how to perform the methods of claim 1 and provided a working example.

Applicants also remind the Examiner that the claims of the parent '239 patent, of which the present application is a continuation and thus has the same disclosure, are drawn to a method of treatment in a human patient using allogeneic MSCs.

Claims 11-16 were rejected as encompassing a method of treating a human subject for promoting growth of any muscle by administering allogeneic MSCs.

In response, Applicants note that the parent application (now the '239 patent) contains a similar claim (claim 1) directed to connective tissue and that the Examiner has found claims 11-16 to be an obvious variation of the claims of the '239. In addition, Applicant has defined the term "connective tissue" to include muscle (see the application at page 5, lines 17-19). In addition, with the disclosure regarding MSCs as provided in the Application, Applicants fail to see why the process that works so well with other types of connective tissue would be questioned regarding this specific embodiment.

Claims 17-19 were rejected as promoting connective tissue implantation by adhering allogeneic MSCs onto a connective tissue surface of a prosthetic device.

In response, Applicants note that this is a procedure similar to that of claims 1 and 11. It seems of little import whether the connective tissue is on a prosthetic device when implanted into the recipient or not. The important matter is that the MSCs are administered and are able to differentiate into the desired type of tissue. (See, for example, the application at page 5, lines 7-20 (or the '239 patent at column 2, line 58, over to column 3, line 9, including the '985 patent disclosed therein). Also important is that no prior MHC matching step is required and this has been added to the claim to make certain that the process is understood.

Rejection Under 35 U.S.C. 103

Claims 11-16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan and Haynesworth (U.S. Pat. No. 5,226,914, issued 13 July 1993) in view of Bruder et al (J. Cell Biochem. (1994)), Nevo et al. (Cell Transplantaion (1998)), Robinson et al (Agents Actions (1993)), Stiller et al (N. Eng. J. Med. (1976)) and Kessinger (Apheresis (1990)), in view of Theobald et al (Transplantation (1993)).

A finding of obviousness requires three conditions:

1. The cited references, in light of the then available general knowledge, must suggest the combination of the references to produce the claimed invention [see: *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)].

2. Combination or modification of the references must have a reasonable expectation of success. [See: *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991)]

3. Combination of the cited references must teach or suggest all of the limitations of the claim(s) [See: *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)]

Initially, Applicants note that the Examiner has rejected these claims based on a large number of references (a total of 7).

The Examiner relies on Caplan and Haynesworth as teaching a method of treating skeletal and other connective tissue disorders in humans using culturally expanded marrow-derived mesenchymal stem cells (MSCs) and various methods for isolation, etc.

In response, Applicants direct the Examiner's attention to claim 11 (and the claims dependent therefrom). Claim 11, as currently amended, recites a method for

promoting muscle tissue growth by administering allogeneic mesenchymal stem cells where a step of MHC matching of the donor human subject is not employed prior to the administration of allogeneic mesenchymal stem cells to the recipient. None of the cited references even mentions such a radical departure from accepted procedures.

As stated in the application at page 1, last paragraph, "the mesenchymal stem cells are immunologically neutral and therefore can be used as described herein without inducing an adverse immune response in the recipient of the cells." Since this was not previously known, there was no reasonable expectation that allogeneic mesenchymal stem cells could be used without provoking an adverse immune response associated with the use of such material. The Examiner has cited no references suggesting such a procedure. Simply put, at the time this application was filed, the claimed invention would not have been expected to be therapeutically feasible. The Caplan and Haynesworth patent merely looks to isolating and culturally expanding mesenchymal cells for use in treating connective tissue disorders and says nothing about muscle tissue growth or the ability to utilize MSCs without prior MHC matching.

Applicants have already noted that muscle is considered under the general term of connective tissue, as recited in the application at 5, lines 17-18, and this procedure, without using prior matching, would not have been expected to work for muscle tissue any more than any other type of connective tissue.

The remaining prior art does not teach or suggest, either individually or however the references are combined, that allogeneic mesenchymal stem cells are "invisible" and can be used without an adverse immune response, or can be used to treat a recipient in need of muscle tissue growth or that such treatment can be used without prior MHC matching, all of which are taught only by Applicants.

The Examiner relies on Bruder et al (1994) to show repair of bone and skeletal regeneration therapy using mesenchymal stem cells. However, the Bruder et al

reference is basically a review article that, by its own terms, relates to use of autologous mesenchymal stem cells and not allogeneic cells (from a different individual). This reference does not even use the word "allogeneic."

The Examiner's reliance on Nevo et al is equally unavailing because that reference is directed to skeletal tissue and not muscle and does not even mention the absence of a prior matching step.

The Examiner has also relied on Robinson et al (1993) as teaching the use of fetal allogeneic mesenchymal stem cells in the repair of cartilage. In fact, this reference teaches away from such use and any use for repair of cartilage is demonstrated only with DOTCs derived from autologous adult animals. [See: page 232, starting at the 8th line from the bottom: "The mesh was later implanted into prepared defects in the articular cartilage of autogenic animals." (emphasis added)] No other types of treatments are disclosed.

Further, at page 234 of Robinson et al, there is an experiment performed with goats wherein it is stated that the DOPC cells were prepared in the same manner as the earlier cells so that the cells were undoubtedly autologous.

On page 235 of the Robinson et al paper, it is stated, starting at line 14, that the DOTCs are the preferred cells and that such autogenic cells are advantageous because they decrease the possibility of an immune reaction. Thus, this paper would actually deter those in the art from using allogeneic cells. The lack of a prior MHC matching step is irrelevant because no allogeneic cells are used.

The Examiner cites Stiller et al (1976) as teaching a method of testing an immune response and that humoral and cellular response have a decisive role in the acceptance or rejection of allogeneic grafts. However, this in no way helps to achieve Applicants' teaching because Stiller does not disclose or suggest that allogeneic

mesenchymal stem cells are "invisible" to the immune system. He only provides a means of testing immune response and this is irrelevant to the present invention because Applicants have discovered that MHCs are immunologically invisible and therefore no testing is required. That is why the claim reciting a method that does not employ a matching step is patentable (and was patentable for connective tissue in the parent case that issued as a patent – see claim 1 of the '239 patent relied on by the Examiner for a double patenting rejection).

The net contribution of the Stiller et al teaching is best stated in their own words on page 981, right column, final paragraph, that, "Our study indicates that assays are available that correlate with and anticipate graft rejection over extended periods in the clinical course of the transplant. It is now possible to delineate periods when the recipient is more responsive immunologically and to predict with confidence ($P<0.001$) the occurrence of a rejection episode. It should be possible to tailor immunosuppressive therapy to a particular response of the recipient and to begin therapy before damage of the target-organ graft occurs." Stiller only teaches a method to "predict" when adverse reactions will occur – but adverse reactions don't occur when Applicants' method is used so Stiller et al. is irrelevant. The cells of the invention do not show the kind of effects Stiller et al wants to reveal, *i.e.*, rejection episodes.

Further, the Caplan and Stiller references cannot be used together because Caplan discloses the use of the patient's own cells (see Example 2C of Caplan at column 16, lines 49-56). That being so, there would be no immune response and thus no reason to "predict" rejection episodes using the Stiller teaching. Therefore, there is no motivation to combine the references.

As to Kessinger, the Examiner is quite correct in stating that this Abstract teaches intravenous administration of autologous hematopoietic stem cells. [See: page 4 of the Office Action, first full paragraph] However, the present application is directed to the use of mesenchymal stem cells that are allogeneic.

In sum, there is no motivation to combine these references to achieve the Applicants' invention because, even if they were combined, they could not achieve it. Most of the references are directed to autologous cells and none of them suggest using allogeneic cells without prior matching.

"Obviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." [*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 USPQ 929, at 933 (Fed Cir 1984)]

As stated by the Board Of Patent Appeals and Interferences, in reversing a rejection for obviousness in a case dealing with a method for increasing the proportion of plant mutants in succeeding generations, "the Examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness...That which is within the capabilities of one skilled in the art is not synonymous with obviousness." [*Ex parte Levengood*, 28 USPQ2d 1300, at 1301 (1993).

The Theobald et al paper also fails to support obviousness when combined with the other references. Theobald et al teach only use of allogeneic differentiated cells *in vitro* {Abstract, first sentence] that possess only MHC I surface antigens [Theobald at page 131, column 1, first full paragraph] and "lack as yet undefined co-stimulatory factors required for their recognition as foreign." [Theobald et al, page 128, column 2, last full paragraph] Unlike the teaching of the application, Theobald nowhere mentions use of any kind of stem cells or that such cells can differentiate into mature cells that are themselves immunologically neutral. Theobald et al also suggest that their results might have been due to loss of accessory molecules [page 132, column 1, lines 1-5].

Put simply, Applicants respond that the cited references fail to show obviousness regardless of how they are combined, that they contain no suggestion to combine them but actually teach away from such combination and that any such combination would lack any realistic expectation of success.

Claims 1 and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan and Haynesworth (U.S. Pat. No. 5,226,914, issued 13 July 1993) in view of Bruder et al (J. Cell Biochem. (1994)), Nevo et al. (Cell Transplantaion (1998)), Robinson et al (Agents Actions (1993)), Stiller et al (N. Eng. J. Med. (1976)), Theobald et al (Transplantation (1993)) and Kessinger (Apheresis (1990)), and further in view of Gerson et al (U.S. Pat. No. 5,591,625, issued 7 January 1997).

In response, Applicants believe that the recitation as to claims 11-16 above is equally applicable with respect to claim 1.

Thus, claim 1 provides appropriate examples, as already disclosed and has been further amended to recite that a prior matching step is not employed.

Claim 15 is drawn to intravenous administration. If the Examiner's contention is that cells can be administered intravenously, that is already well known. However, claim 15 is directed to intravenous administration of the allogeneic mesenchymal stem cells disclosed according to the present invention. It would not be obvious to use intravenous administration of the cells of the invention because it would not have been obvious to administer allogeneic cells at all unless a prior matching step is employed, absent Applicants' teaching.

Applicants wonder if the Examiner might have meant claim 17 instead. Applicants note that claim 17 has been amended to recite that a prior matching step is

not employed and that the arguments already presented regarding claims 11-16 apply equally here.

A review of the added Gerson reference indicates this is drawn to use of allogeneic recombinant cells, in which case Applicants believe that the Examiner may have meant claim 10. If so, Applicants respectfully traverse the Examiner's argument regarding the use of allogeneic mesenchymal stem cells expressing exogenous genetic material. The Examiner's argument appears to be that because it is possible to transduce animal mesenchymal stem cells with exogenous genetic material it therefore renders obvious the aspect of the present invention directed to use of allogeneic recombinant cells.

However, that is simply not the case. Although Gerson includes generic claims, the presence of generic claims does not render obvious the use of allogeneic cells, as claimed. With respect to the use of allogeneic cells, as claimed, Gerson is no more pertinent than the Caplan patent in that Gerson does not disclose or suggest that mesenchymal stem cells do not produce an adverse immune response. In fact, Gerson states "Patient preparation for introduction of mesenchymal stem cells includes, but is not limited to...(c) immunosuppression in the setting of allogeneic cell therapy." [See column 2, lines 62-67]. No one but the inventors of the present invention have discovered the ability to use allogeneic cells without prior matching. Since, as Applicants have already demonstrated, it would not have been obvious to transplant allogeneic mesenchymal stem cells not having genetic modification, it would be equally unobvious to transplant such cells following genetic modification.

In sum, there is no motivation to combine these references because each talks about use of either autologous cells (Caplan, Bruder, Robinson, Kessinger), which require no immunosuppression, or the use of immunosuppression (Stiller), which is not needed where autologous cells are used. Further, even if these references are combined, they would suggest only the use of autologous cells, or allogeneic

differentiated fetal cells, to repair tissue damage and not the use of either stem cells in general, or MSCs in particular.

Because all of the claims of the invention recite use of allogeneic mesenchymal stem cells, the references also do not suggest, in any combination, all of the limitations of the claims and thus fail under condition three mentioned above.

In view of the foregoing response and amendments, Applicants believe that the grounds of rejection have been overcome and respectfully request that the Examiner reconsider the rejection.

Applicants have included herewith a request for a 2 month extension of time to respond and a check covering all fees for a small entity. No additional fee is believed due in filing the above amendment. The Commissioner is requested to charge any additional fees, or credit any refunds, to Deposit Acc't No. 03-0678.

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